

Attorney Docket No.: 330310.00101  
Customer No. 27160

U.S. Patent Application No.  
10/669,441

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Re Application of:

Leland SHAPIRO

Application No.: 10/669,441

Filed: September 25, 2003

For: INHIBITORS OF SERINE PROTEASE  
ACTIVITY, METHODS AND  
COMPOSITIONS FOR TREATMENT  
OF NITRIC OXIDE INDUCED  
CLINICAL CONDITIONS

:  
:  
: Group Art Unit: 1614  
:  
: Examiner: Not Yet Assigned  
:  
: Confirmation No.: 4274  
:  
: Atty. Dkt. No.: 330310.00101

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

February 8, 2005

**INFORMATION DISCLOSURE STATEMENT**

Dear Sir:

In compliance with the duty of disclosure under 37 C.F.R. §1.56 and in accordance with the practice under 37 C.F.R. §§1.97 and 1.98, the Examiner's attention is directed to the documents listed on the enclosed Forms PTO/SB/08A and PTO/SB/08B. Please note that these documents were all considered in related application 09/518,097, filed March 3, 2000; now U.S. Patent No. 6,489,308, issued December 3, 2002. For the convenience of the Examiner a partial copy of the above patent with the listed references is enclosed. The citation numbers have been marked on the patent for ease of comparison.

**FORMAL MATTERS**

In accordance with 37 C.F.R. § 1.97(b)(3), since a first Official Action on the merits of the subject application has not yet been issued, neither a certificate, petition nor payment of a fee is believed to be required for this Information Disclosure Statement. However, the Commissioner is hereby

Attorney Docket No.: 330310.00101  
Customer No. 27160



U.S. Patent Application No.  
10/669,441

authorized to charge any fee which may be required in connection with this paper to Deposit Account No.  
50-1710.

CONCLUSION

It is respectfully requested that the above information be considered by the Examiner and that a copy of the enclosed Forms PTO/SB/08A and PTO/SB/08B be returned indicating that such information has been considered.

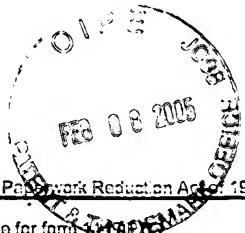
Applicant's undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3500. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Serge Sira", written over a horizontal line.

Serge Sira, PH.D.  
Attorney for Applicant  
Registration No. 39,445

Patent Administrator  
KATTEN MUCHIN ZAVIS ROSENMAN  
525 West Monroe Street, Suite 1600  
Chicago, Illinois 60661-3963  
(202) 625-3500



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**Complete if Known**

Application Number	10/669,441
Filing Date	September 25, 2003
First Named Inventor	Leland SHAPIRO
Art Unit	1614
Examiner Name	Not Yet Assigned
Attorney Docket Number	330310.00101

Sheet 1 of 17

**U. S. PATENT DOCUMENTS**

Examiner Initials*	Cite No. <sup>1</sup>	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code <sup>2</sup> (if known)			
	1	US- 4,021,472 A	05/1977	Fujii et al.	
	2	US- 4,051,842 A	10/1977	Hazel et al.	
	3	US- 4,140,122 A	02/1979	Kuhl et al.	
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	18	US- 4,843,094 A	06/1989	Imaki et al.	
	19	US- 4,889,723 A	12/1989	Kim et al.	

**FOREIGN PATENT DOCUMENTS**

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		Country Code <sup>3</sup> Number <sup>4</sup> Kind Code <sup>5</sup> (if known)				
	20	WO 94/07525	04/1994			
	21	WO 95/28422	10/1995			
	22	WO 95/34538	12/1995			
	23	WO 96/12021	04/1996			
	24	WO 96/14067	05/1996			
	25	WO 97/03679	02/1997			

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	26	US- 4,931,279 A	06/1990	Bawa et al.	
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	28	US- 5,004,612 A	04/1991	Kim et al.	
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	33	US- 5,175,253 A	12/1992	Fallon et al.	
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	35	US- 5,216,022 A	06/1993	Oleksyszyn et al.	
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	39	US- 5,416,191	05/1995	Cheronis et al.	
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	45	WO 97/09346	03/1997			
	46	WO 97/09347	03/1997			
	47	WO 97/10222	03/1997			
	48	WO 97/10231	03/1997			
	49	WO 97/21690	06/1997			
	50	WO 97/24339	07/1997			

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Attorney Docket Number	330310.00101

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	51	US- 5,486,470 A	01/1996	Darke et al.	
	52	US- 5,489,593 A	02/1996	Palmer et al.	
	53	US- 5,504,094 A	04/1996	Nakane et al.	
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	70	WO 97/31937	09/1997			
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	76	US- 5,663,416 A	09/1997	Kirschenheuter et al	
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	78	US- 5,700,779 A	12/1997	Goodfellow et al.	
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	80	US- 5,712,117 A	01/1998	Sprecher	
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	82	US- 5,750,506 A	05/1998	Goodfellow et al.	
	83	US- 5,759,548 A	06/1998	Bathurst et al.	
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	85	US- 5,798,442 A	08/1998	Gallant et al.	
	86	US- 5,801,148 A	09/1998	Gyorkos et al.	
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	95	WO 98/06417	02/1998			
	96	WO 98/09206	03/1998			
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	98	WO 98/21186	05/1998			
	99	WO 98/22098	05/1998			
	100	WO 98/22619	05/1998			

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	101	US- 5,861,380 A	01/1999	Gyorkos et al.	
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	112	WO 98/23565	06/1998			
	113	WO 98/24806	06/1998			
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	115	WO 98/49190	11/1998			
	116	WO 98/50342	11/1998			
	117	WO 98/50420	11/1998			

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	119	WO 97/41231	08/1999			
	120	WO 99/43308	09/1999			
	121	WO 00/52034	09/2000			

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				Application Number	10/669,441
				Filing Date	September 25, 2003
				First Named Inventor	Leland SHAPIRO
				Art Unit	1614
				Examiner Name	Not Yet Assigned
Sheet	7	of	17	Attorney Docket Number	330310.00101

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	122	Aoki H, Akaike T, Abe K, Kuroda M, Arai S, Okamura R, Negi A, Maeda H. Antiviral effect of oryzacystatin, a proteinase inhibitor in rice, against herpes simplex virus type I in vitro and in vivo. Antimicrob Agents Chemother Apr. 1995; 39(4):846-9.	
	123	Auerswald et al., "Recombinant leech-derived trypsin inhibitor: construction, production, protein chemical characterization and inhibition of HIV-1 replication", Biol Chem Hoppe Seyler, 375(10):695-703 (1994).	
	124	Avril LE, Di Martino-Ferrer M, Barin F, Gauthier F., "Interaction between a membrane-associated serine proteinase of U-937 monocytes and peptides from the V3 loop of the human immunodeficiency virus type I (HIV-1) gp120 envelope glycoprotein", FEBS Lett, 317(1-2):167-72 (Feb. 8, 1993).	
	125	Beal, M.F., "Mitochondria, Free Radicals, and Neurodegeneration", Curr. Opin. Neurobiol., 1996, 6, 661-666.	
	126	Bjorck L, Grubb A, Kjellen L. Cystatin C, a human proteinase inhibitor, blocks replication of herpes simplex virus. J Virol Feb. 1990;64(2):941-3.	
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	132	Flaitz CM, Hicks MJ. "Molecular piracy: the viral link to carcinogenesis." Oral Oncol Nov. 1998;34(6):448-53.	
	133	Griffin, William C., "Calculation of HLB Values of Non-Ionic Sufactants", [H. L. B.--The Hydrophilic-Lipophilic Balance], J. Soc. Cos. Met. Chem., vol. 5, p. 249 (1954).	
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	140	Best, P.J.M., et al., Arterioscler Thromb Vasc Biol 1999, 19, 14.	
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	142	Meylan et al., "HIV infectivity is not augmented by treatment with trypsin, Factor Xa or human mast-cell tryptase", AIDS, 6(1):128-30 (1992).	
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	148	Pellegrini A, Thomas U, Franchini M, Stockli M, Klauser S, Hunziker P, von Fellenberg R. Identification of an aprotinin antiviral domain. FEBS Lett May 16, 1994;344(2-3):261-5.	
	149	Schwartz, et al., "Antiviral activity of the proteasome on incoming human immunodeficiency virus type I", J Virol, 72(5):3845-50 (1998).	
	150	Sichko ZhV, Koslova OL. Experience in treating herpetic infection with trypsin [Article in Russian]. Vrach Delo Mar. 1991;86-9.	
	151	Szeghy G, Kenyeres B. On the therapy of herpes simplex keratitis with heparin and trypsin. [Article in German] Klin Monatsbl Augenheilkd 1968; 153(6):827-30.	

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	152	Cilberto et al., 1985, Cell, 41:531-540.	
	153	Dery O. and Bunnett, N.W. Biochem Soc Trans 1999, 27, 246-254.	
	154	Altieri, D.C. J Leukoc Biol 1995, 58, 120-127.	
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	161	Lowenstein C. J. et al. in Proc. Natl. Acad. Sci. USA, 1993, 90, 9730.	

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	162	Nathan, C. in FASEB J. 1992, 6, 3501.	
	163	Rehman, A. et al. in Br J Pharmacol, 1997, 122, 1702.	
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	172	Schini et al. in Circ Res 1994, 74, 24.	
	173	Meki, A. R. et al. in Toxicon 1998, 36, 18519.	
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	179	Budavari, Susan (Editor), "The Merck Index", An Encyclopedia of Chemicals, Drugs, and Biologicals; Merck & Co., Inc., 11th edition.	
	180	Merrifield, R.B., "Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide", 1963, J. Am. Chem. Soc., (85):2149.	
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	182	Scharpe et al., "Protease and their inhibitors: today and tomorrow", 1991, Biochimie, 73(1):121-126.	
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Sheet	14	of	17	Attorney Docket Number	330310.00101

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
	192	Decroly, et al., "Identification of the paired basic convertases implicated in HIV gp160 processing based on in vitro assays and expression in CD4(+) cell lines", 1996, J Biol Chem, 271(48):30442-50.	
	193	Moulard, et al., "Kex2p: a model for cellular endoprotease processing human immunodeficiency virus type 1 envelope glycoprotein precursor", Eur J Biochem, 1994, 225(2):565-72.	
	194	Avril, et al., "Identification of the U-937 membrane-associated proteinase interacting with the V3 loop of HIV-1 gp120 as cathepsin G", FEBS Lett, 1994, 345(1):81-6.	
	195	Harvima et al., "Separation and partial characterization of proteinases with substrate specificity for basic amino acids from human MOLT-4 T lymphocytes: identification of those inhibited by variable-loop-V3 peptides of HIV-1 (human immunodeficiency virus-1) envelope glycoprotein", 1993, Biochem J, 292 (Pt 3):711-8.	
	196	Bourinbaiar, et al., "Acrosin inhibitor, 4'-acetamidophenyl 4-guanidinobenzoate, an experimental vaginal contraceptive and anti-HIV activity", Contraception, 1995, 51(5):319-22.	
	197	Bristow, et al., "Inhibition of HIV-1 by modification of a host membrane protease", 1995, Int Immunol, 7(2):239-49.	
	198	Bukrinskaia et al., "Inhibition of HIV reproduction in cultured cells using proteolysis inhibitors", 1989, Vopr Virusol, 34(1):53-5.	
	199	Bourinbair, et al., "Effect of serine protease inhibitor, N-alpha-tosyl-L-lysyl-chloromethyl ketone (TLCK), on cell-mediated and cell-free HIV-1 spread", Cell Immunol, 1994, 155(1):230-6.	
	200	Turpin et al., "Human immunodeficiency virus type-1 (HIV-1) replication is unaffected by human secretory leukocyte protease inhibitor", 1996, Antiviral Res, 29(2-3):269-77.	
	201	Kennedy et al., "Submandibular salivary proteases: lack of a role in anti-HIV activity", 1998, J Dent Res, 77(7):1515-9.	

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Substitute for form 1449/PTO  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  <i>(Use as many sheets as necessary)</i>				<b>Complete if Known</b>	
				Application Number	10/669,441
				Filing Date	September 25, 2003
				First Named Inventor	Leland SHAPIRO
				Art Unit	1614
				Examiner Name	Not Yet Assigned
Sheet	15	of	17	Attorney Docket Number	330310.00101

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	202	Premack, B.A. et al., "Chemokine Receptors: Gateways to Inflammation and Infection", 1996, Nature Medicine 2:1174-1178.	
	203	Zhirnov O.P. et al., "Antiviral activity of proteinase inhibitors in cultured cells infected with alpha-viruses", Mol Gen Mikrobiol Virusol, 1985, (12):30-6.	
	204	Chesnokova N.B. et al., "Antiproteases in herpetic keratitis", Metab Pediatr Syst Ophthalmol, 1986;9(1):593-6.	
	205	Adelman S.F. et al., "Protease inhibitors suppress fibrinolytic activity of herpesvirus-transformed cells", J Gen Virol, 1982, 60(Pt 1):15-24.	
	206	Chesnokova N.B. et al., "Main proteolytic inhibitors in ocular herpes", Vopr Med Khim, 1981, 27(5):663-5.	
	207	Sharpstone D. et al., "Faecal alpha 1 antitrypsin as a marker of gastrointestinal disease in HIV antibody positive individuals", Gut, 1996, 38(2):206-10.	
	208	Patel et al., "The Role of Protease Drug During Apoptosis", 1996, FASEB J, 10(5):587-597.	
	209	Estaquier J., "Fas-mediated apoptosis of CD4+ and CD8+ T cells from human immunodeficiency virus-infected persons: differential in vitro preventive effect of cytokines and protease antagonists", 1996, Blood, 15;87(12):4959-66.	
	210	Shimizu, T. et al., "DNA Fragmentation induced by Protease Activation in P53-null Human Leukemia HL60 Cells Undergoing Apoptosis Following Treatment with the Topoisomerase I Inhibitor Camptothecin: Cell-Free System Studies", 1996, Exp Cell Res, 1:226(2):292-301.	
	211	Glynn et al., "Apoptosis induced by HIV Infection in H9 T Cells is Blocked by ICE-Family Protease Inhibition but not by a FAS(CD95) Antagonist", 1996, J. Immunol, 1; 157(7):2754-2758.	

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				Application Number	10/669,441
				Filing Date	September 25, 2003
				First Named Inventor	Leland SHAPIRO
				Art Unit	1614
				Examiner Name	Not Yet Assigned
Sheet	16	of	17	Attorney Docket Number	330310.00101

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	212	Ooka, T., et al., "Protective effects of human urinary trypsin inhibitor against trypsin-induced relaxation in rat aorta", Crit care Med, 1996, 24(11): 1903-1907.	
	213	Novradovsky, A., et al., "Endothelial Nitric Oxide Synthase as a Potential Susceptibility Gene in the Pathogenesis of Emphysema in alpha1-Antitrypsin Deficiency", 1999, Am J Respir Cell Mol Biol, 1:20(3):441-447.	
	214	Cordiali Fei et al., "Behavior of several 'progression markers' during the HIV-Ab seroconversion period. Comparison with later stages", 1992, J Biol Regul Homeost Agents, 6(2):57-64.	
	215	Lima et al., "Mucosal injury and disruption of intestinal barrier function in HIV-infected individuals with and without diarrhea and cryptosporidiosis in northeast Brazil", 1997, Am J Gastroenterol, 92(10):1861-6.	
	216	Banfi et al., "Tumor-associated trypsin inhibitor in induced and acquired immunodeficiency. Studies on transplanted and HIV-infected patients", 1991, Scand J Clin Lab Invest 51, Suppl, 207:55-8.	
	217	Deam et al., "Alpha 1-antitrypsin phenotypes in homosexual men", 1989, Pathology, 21(2):91-2.	
	218	Pezzilli et al., "Serum pancreatic enzymes in HIV-seropositive patients", Dig Dis Sci, 1992, 37(2):286-8.	
	219	Tang et al., "Inactivation of HIV-1 by trypsin and its use in demonstrating specific virus infection of cells", 1991, J Virol Methods, 33(1-2):39-46.	
	220	Glozman, "Immunologic functions of enzyme therapy of patients with orchiepidymitis", 1990, Antibiot. Khimioter, 35(7):50-52.	
	221	Franzusoff, et al., "Biochemical and genetic definition of the cellular protease required for HIV-1 gp160 processing", 1995, J Biol Chem, 270(7):3154-9.	

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**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**

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**Complete if Known**

Application Number	10/669,441
Filing Date	September 25, 2003
First Named Inventor	Leland SHAPIRO
Art Unit	1614
Examiner Name	Not Yet Assigned
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Sheet	17	of	17
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	222	Gu et al., "Furin is important but not essential for the proteolytic maturation of gp160 of HIV-1", FEBS Lett. 1995, 365(1):95-7.	
	223	Bukrinskaia A.G., "Suppression of rotavirus SA-11 reproduction by protease inhibitors in cell culture", Vopr Virusol, 1987, 32(1):71-4.	

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